--~~25~~. (amended) A method for treating vagally induced sinus bradycardia which comprises administering, by the intravenous or oral routes, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims [13] ~~29~~, [14] ~~30~~, ~~15~~, ~~16~~, ~~18~~, ~~19~~, ~~20~~, ~~21~~ or ~~22~~.--

--~~26~~. (amended) A pharmaceutical composition, for administration by inhalation, suitable for the treatment of chronic obstructive bronchitis or slight to moderately severe asthma, which comprises a compound in accordance with claims [13] ~~29~~, [14] ~~30~~, ~~15~~, ~~16~~, ~~18~~, ~~19~~, ~~20~~, ~~21~~ or ~~22~~.--

--~~27~~. (amended) A pharmaceutical composition, for oral administration, suitable for the treatment of vagally induced sinus bradycardia, which comprises a compound in accordance with claims [13] ~~29~~, [14] ~~30~~, ~~15~~, ~~16~~, ~~18~~, ~~19~~, ~~20~~, ~~21~~ or ~~22~~.--

--~~28~~. (amended) A pharmaceutical composition, for intravenous administration, suitable for the treatment of vagally induced sinus bradycardia, which comprises a compound in accordance with claims [13] ~~29~~, [14] ~~30~~, ~~15~~, ~~16~~, ~~18~~, ~~19~~, ~~20~~, ~~21~~ or ~~22~~.--

In the Abstract of the Disclosure

Delete the current abstract and replace it with the new abstract shown on the separate sheet which is attached to this response.

REMARKS

Claims 13-28 were pending. Claims 13 and 14 have been canceled and claims 29 and 30 have been added. Thus, claims 15-30 are now pending.

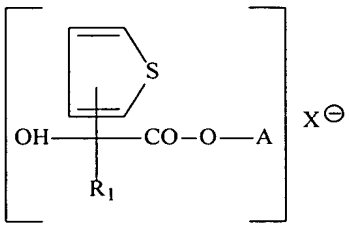
The allowance of claims 17, 18, 19 and 21 is noted with sincere appreciation.

It is noted that the allowed claims are directed to specific compounds. The claims which remain to be allowed are generic.

Claim 13 has been rejected under 35 USC 112, second paragraph, because the "last listed Q group is incorrect since it has too many valances for the ring carbon atoms in the epoxide ring. The Examiner is appreciated for having spotted and called attention to this typographical error. In order to overcome this rejection, claim 13 has been canceled and replaced with new claim 29. In claim 29 the last Q group has been corrected, so that it is now the following:

ABSTRACT OF THE DISCLOSURE

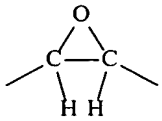
--Compounds of the formula



of which, in exemplary compounds, the thienyl group is attached via the 2-position and:

(a) A is 3α-(6β, 7β-epoxy)-tropanyl methobromide and R_1 is 2-thienyl;
(b) A is 3α-(6, 7dehydro)-tropanyl methobromide and R_1 is 2-thienyl;
(c) A is 3β-tropanyl methobromide and R_1 is 2-thienyl; and,
(d) A is 3α-(N-isopropyl)-nortropanyl methobromide and R_1 is cyclopentyl.

These are anticholinergics. Administered by inhalation, they are useful for the treatment of chronic obstructive bronchitis or slight to moderately severe asthma. Administered by the intravenous or oral routes, they are useful for the treatment of vagally induced sinus bradycardia.--



The correction of the structure for the last Q group in claim 29 does not introduce new matter. The correct structure is depicted on the bottom of page 1 of the specification.

Claim 14 has been rejected under 35 USC 112, second paragraph, because the "second listed R group is incorrect for having too many hydrogens on the carbon atom". Again, the Examiner is appreciated for having spotted and called attention to this typographical error. In order to overcome this rejection, claim 14 has been canceled and replaced with new claim 30. In claim 30 the second listed R group has been corrected, so that it is now C_2H_5, rather than CH_2H_5. The correction of the structure for R does not introduce new matter. The correct structure is depicted on line 5 of page 3 of the specification.

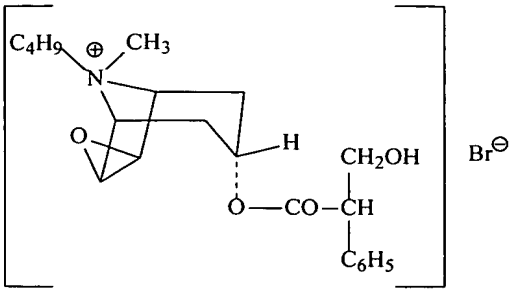
The specification has been objected to under 35 USC 112, first paragraph, as failing to describe the species of new claims 20 and 22. Claims 20 and 22 have been rejected for the same reason. In response it is noted that claims 20 has been amended so that the definition of A is now 3α-(6, 7-dehydro)-tropanyl methobromide rather than 3α-(6 β, 7β-dehydro)-tropanyl methobromide. Claim 20, as amended, is concordant with Example 3 of Table II of the specification. Claim 22 has been amended so that the definition of A is now cyclopentyl rather than cyclopropyl. Claim 22, as amended, is concordant with Example 31 of Table II.

Claims 23-28 are rejected because they depend from rejected base claims 13, 14, 20 and 22. To overcome this basis for rejection, claims 23-28 have been amended so that they now depend from claims 29 and 30 rather than claims 13 and 14. Claims 29 and 30 are believed to be allowable. Claims 20 and 22 are also believed to be allowable as amended.

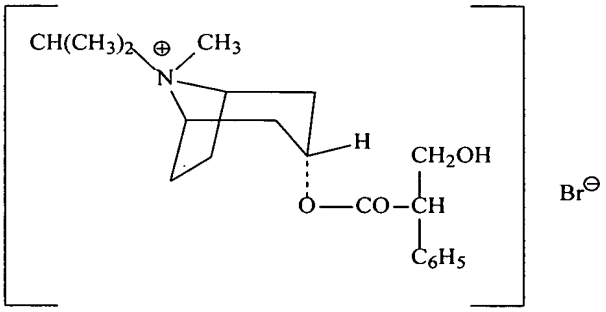
The abstract has been objected to under 35 USC 132, as introducing new matter. Specifically, compounds (b) and (d) are deemed to be new matter. To overcome this ground of objection, the abstract has been amended. As amended, compounds (b) and (d) correspond to compounds 3 and 31 of Table II, and no new matter is introduced.

Claims 13-16 and 23-28 are rejected under 35 USC 103 as being unpatentable over the Merck Index descriptions of the compounds N-butylscopolammonium bromide and ipratropium bromide, in view of Grimminger et al. (As claims 13 and 14 have been replaced with new claims 29 and 30, the rejection is viewed as pertaining to claims 29, 30, 15, 16 and 23-28.)

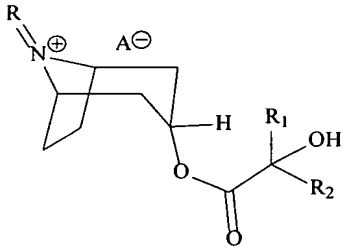
N-butylscopolammonium bromide is a compound of the following structural formula:



Ipratropium bromide is a compound of the following structural formula:



The secondary reference, Grimminger et al., teaches 3-tropanol esters of the general formula



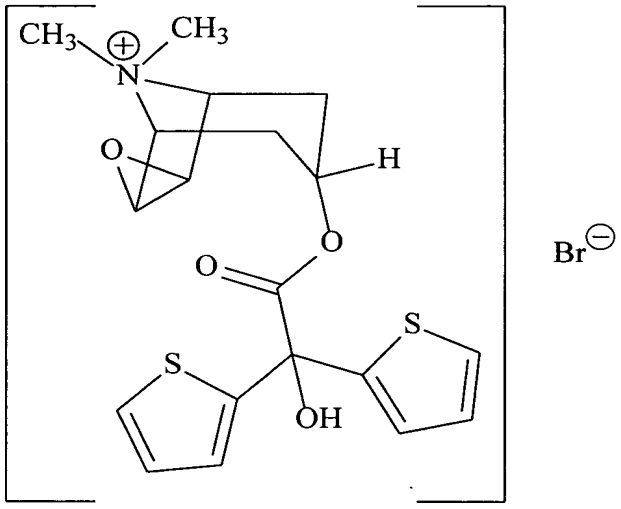
wherein, R is ,inter alia, C_3-C_9 alkylene, and R_1 and R_2 are the same or different and are, inter alia, cyclohexyl, phenyl or thienyl. Specifically disclosed are compounds wherein R_1 and R_2 are both phenyl and R and the nitrogen atom to which it is attached, in a spiro system, together form, inter alia, pyrrolidin-1-yl (Example 1); pyrrolidin-3-yl (Example 2); isoindol-2-yl (Example 3); and, morphlin-4-yl (Example 4).

It is apparently the Examiner's position that N-butylscopolammonium bromide, ipratropium bromide and the compounds of Grimminger are all of the same pharmacological class (antispasmodics and/or broncholytics), and that one skilled in the art would, therefore, find motivation to take the tropanol portions from N-butylscopolammonium bromide and ipratropium bromide and combine these with the acid moieties of Grimminger, to obtain compounds within the scope of generic claims 29, 30, 15 and 16, thus establishing *prima facie* structural obviousness.

The examiner has suggested, indirectly, that prima facie structural obviousness could be overcome by showing that compounds within the scope of the genera defined by claims 29, 30, 15 and 16 possess unexpected properties, such as, for example, unexpectedly potency as broncholytics.

In fact, it can be demonstrated that the compounds of claims 29, 30, 15 and 16 possess unexpected properties. More specifically, it can be demonstrated that the compounds of the claims under discussion exhibit a duration of action which is far greater than that exhibited by either ipratropium bromide or N-butylscopolammonium bromide. The much improved duration of action of the compounds of the invention is quite unexpected, and it is what makes them patentable over the art cited.

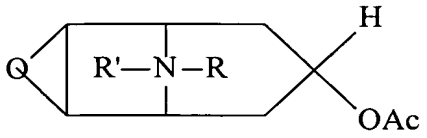
Thus, for example, the duration of activity of one representative compound in accordance with the invention, code-named BA 679 BR, which has the following structure

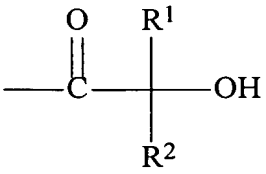


has been compared to that of ipratropium bromide, via tests run in the dog, wherein brochospasm is induced using acetylcholine. BA 679 Br and ipratropium bromide were administered to the test animals via aerosol inhalation and at several dosages. The ability these two drugs to inhibit the induced bronchospasm was measured as a function of dosage and time after administration. The results of this testing are depicted in Graphs 1 and 2 which are attached to this response. It can easily be seen that the representative compound of the invention, BA 679 Br, exhibited a duration of action in this test, at all dosages, which far surpassed that exhibited by ipratropium bromide.

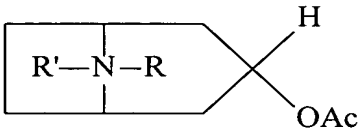
To show that the property of prolonged duration of action is possessed by not only BA 679, but generally by all compounds within the scope of the claims, the applicants have tested a wide array of compounds in accordance with the invention in a rabbit model. In this model, bronchospasm is induced in a test animal through the administration of acetylcholine. A test compound (3 μg/kg) is then administered to each animal intravenously, and the degree to which bronchospasm is inhibited as a

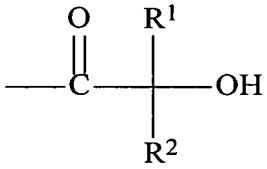
function of time is measured. The results depicted in the following tables have been obtained from such testing.



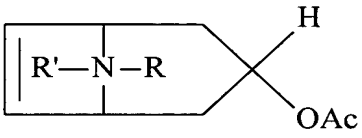
Ac= 

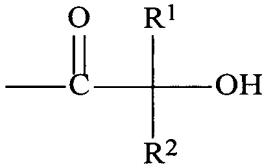
R	R'	R_1	R_2	duration	% inhibition
CH_3	CH_3	2-thienyl	2-thienyl	300 min.	76
CH_3	CH_3	2-thienyl	3-thienyl	300 min.	76
CH_3	CH_3	2-thienyl	phenyl	300 min.	60
CH_3	CH_3	3-thienyl	phenyl	300 min.	81
CH_3	CH_3	2-thienyl	cyclopropyl	300 min.	42
CH_3	CH_3	2-thienyl	cyclohexyl	300 min.	48
CH_3	CH_2H_5	2-thienyl	phenyl	300 min.	29



Ac= 

R	R'	R_1	R_2	duration	% inhibition
i-C_3H_7	CH_3	2-thienyl	phenyl	300 min.	76
CH_3	CH_3	2-thienyl	cyclopentyl	300 min.	69
CH_3	CH_3	2-thienyl	phenyl	300 min.	54
CH_3	CH_3	2-thienyl	cyclopentyl	300 min.	32
CH_3	CH_3	2-thienyl	cyclopentyl	300 min.	23



Ac= 

R	R'	R_1	R_2	duration	% inhibition
CH_3	CH_3	2-thienyl	2-thienyl	300 min.	61
CH_3	CH_3	2-thienyl	3-thienyl	300 min.	68
CH_3	CH_3	2-thienyl	phenyl	300 min.	39

While applicants do not have readily at hand any test data which directly compares the compounds of the invention to N-butylscopolammonium bromide (Buscopan®), they do have data which compares the duration of activity of ipratropium bromide to that of N-butylscopolammonium bromide. This data, which was obtained from an anaesthetized guinea pig model, wherein chemically induced bronchospasm is

inhibited by the administration, by inhalation, of the test compound, is depicted in the following table.

% Inhibition of Bronchospasm				
time after administration	ipratropium bromide 0.1%	Buscopan® 0.3%	Buscopan® 1.0%	Buscopan® 3.0%
1 min.	30 ± 10	20	35 ± 11.0	83 ± 7.3
5 min.	54 ± 7	0	12 ± 10.3	40 ± 4.7
10 min.	71 ± 6	0	0	17 ± 10.3
30 min.	84 ± 6	-	-	8 ± 6.0
60 min.	70 ± 8	-	-	-

It can be seen that ipratropium bromide exhibits a far longer duration of action than does N-butylscopolammonium bromide (Buscopan®). Since the compounds of the invention exhibit a far longer duration of action than does ipratropium bromide, it stands to reason that they would, if tested, also exhibit a even longer duration of action than N-butylscopolammonium bromide (Buscopan®).

Thus, it has been demonstrated that the compounds of the invention exhibit a far greater duration of action than do ipratropium bromide or N-butylscopolammonium bromide (Buscopan®). There is no teaching in the prior art which would lead one skilled in the art to expect that combining the tropanol portions from N-butylscopolammonium bromide and ipratropium bromide (which both have relatively modest duration of action) with the acid moieties of Grimminger would yield compounds having such markedly enhanced duration of action. Accordingly, the compounds of the invention possess unexpected properties which make them unobvious over the prior art.

The applicants stand ready to present the above-described comparative test data in the form of a Rule 132 declaration, should the Examiner find it persuasive.

Summary: On the basis of the foregoing, it is respectfully urged that the new claims now pending (15-30) are supported by the disclosure and patentable over the art thus far made of record. Allowance of the claims and the application as a whole is respectfully requested.

List of Attachments:

(1) Revised Abstract
(2) Graphs 1 and 2
(3) Petition Under 37 CFR 1.136(a) For Extension Of Time

Respectfully submitted,

Alan Stempel
Reg. No. 28,991

January 22, 1996
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I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to:

Assistant Commissioner for Patents
Washington, DC 20231

on January 22, 1996

By: Alan Stempel
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